

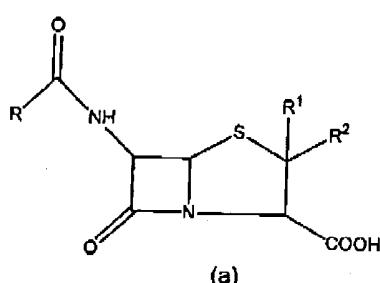
Application No.: 09/457,926
Attorney Docket No.: 9210.0004-00

AMENDMENTS TO THE SPECIFICATION:

Please amend the paragraph beginning on page 4, line 27 and ending on page 7, line 10 with:

More preferably, each ligand that is a beta lactam antibiotic and is selected from the group consisting of:

(i) a compound of formula (a):

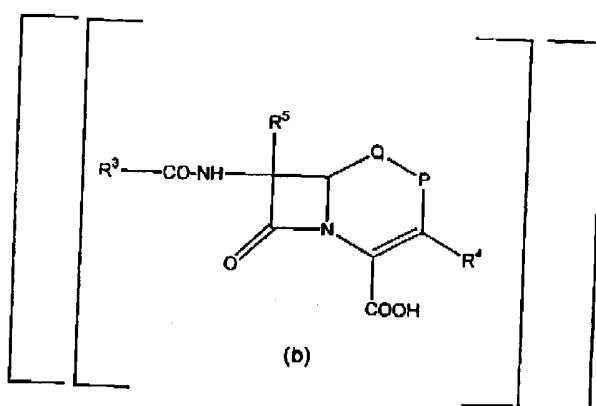


wherein:

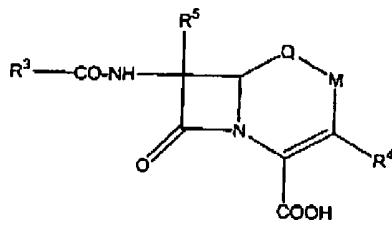
R is substituted alkyl, aryl, aralkyl, or heteroaryl wherein each of said substituent optionally links (a) to a linker via a covalent bond or R is a covalent bond that links (a) to a linker; and

R¹ and R² are, independently of each other, alkyl or at least one of R¹ and R² is a covalent bond linking (a) to a linker;

(ii) a compound of formula (b):



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(b)

wherein:

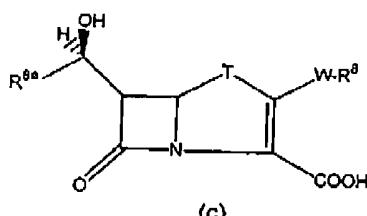
one of [[P]] M and Q is O, S, or -CH₂- and the other is -CH₂-;

R³ is substituted alkyl, heteroarylalkyl, aralkyl, heterocyclalkyl, or -C(R⁶)=NOR⁷ (where R⁶ is aryl, heteroaryl, or substituted alkyl; and R⁷ is alkyl or substituted alkyl) wherein each of said substituent optionally links (b) to a linker or R³ is a covalent bond that links (b) to a linker; and

R⁴ is hydrogen, alkyl, alkenyl, substituted alkenylene, substituted alkyl, halo, heteroarylalkyl, heterocyclalkyl, -SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) or -CH₂SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (b) to a linker or R⁴ is a covalent bond that links (b) to a linker;

R⁵ is hydrogen, hydroxy, or alkoxy;

(iii) a compound of formula (c):



(c)

wherein:

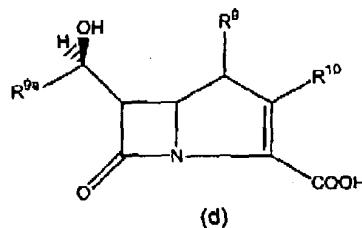
T is S or CH₂

R^{8a} is alkyl;

W is O, S, -OCH₂-, or CH₂; and R⁸ is -(alkylene)-NHC(R^b)=NH where R^b is a covalent bond linking (c) to a linker; or -W-R⁸ is a covalent bond that links (c) to a linker;

(iv) a compound of formula (d):

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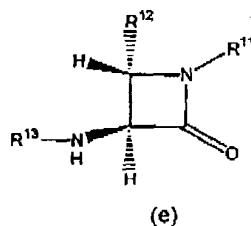
wherein:

R^9 and R^{9a} are alkyl;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, halo, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl or $-CH_2SR^a$ (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (d) to a linker or at least one of R^9 and R^{10} is a covalent bond that links (d) to a linker; or

R^9 and R^{10} together with the carbon atoms to which they are attached form an aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, or heterocyclyl ring of 4 to 7 ring atoms wherein one of the ring atoms optionally links (d) to a linker; or

(v) a compound of formula (e):



wherein:

R^{11} is $-SO_3H$ or $-(alkylene)-COOH$;

R^{12} is alkyl, substituted alkyl, haloalkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, substituted cycloalkyl, or heterocyclyl wherein each of said substituent optionally binds (e) to a linker or R^{12} is a covalent bond that links (e) to a linker;

and

R^{13} is alkyl, acyl, or $-COC(R^{14})=N-OR^{15}$ wherein R^{14} is aryl, heteroaryl which optionally links (e) to a linker, and R^{15} is $-(alkylene)-COOR^{16}$ wherein R^{16} is hydrogen or

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optionally links (e) to a linker or R^{13} is a covalent bond that links (e) to a linker; and pharmaceutically acceptable salts thereof;

Please amend the paragraph beginning on page 39, line 16 and ending on page 48, line 8 with:

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula (I) are preferred.

(A) One preferred group of compounds is a multibinding compound of Formula (II):

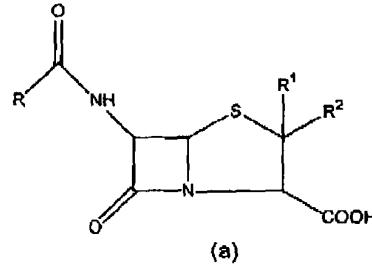
L^a-X-L^b

(II)

wherein:

L^a is a beta lactam antibiotic and is selected from the group consisting of:

(i) a compound of formula (a):



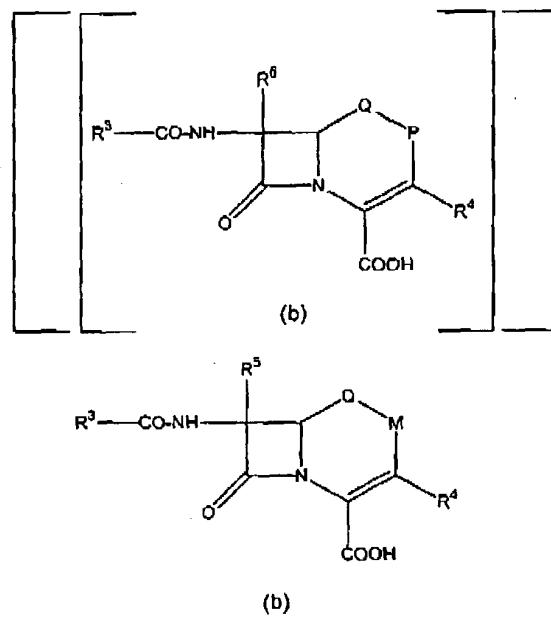
wherein:

R is substituted alkyl, aryl, aralkyl, or heteroaryl wherein each of said substituent optionally links (a) to a linker via a covalent bond or R is a covalent bond that links (a) to a linker; and

R^1 and R^2 are, independently of each other, alkyl or at least one of R^1 and R^2 is a covalent bond linking (a) to a linker;

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(ii) a compound of formula (b):



wherein:

one of [[P]] M and Q is O, S, or -CH₂- and the other is -CH₂-;

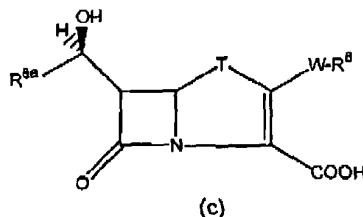
R³ is substituted alkyl, heteroarylalkyl, aralkyl, heterocyclalkyl, or -C(R⁶)=NOR⁷ (where R⁶ is aryl, heteroaryl, or substituted alkyl; and R⁷ is alkyl or substituted alkyl) wherein each of said substituent optionally links (b) to a linker or R³ is a covalent bond that links (b) to a linker; and

R⁴ is hydrogen, alkyl, alkenyl, substituted alkenylene, substituted alkyl, halo, heteroarylalkyl, heterocyclalkyl, -SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) or -CH₂SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (b) to a linker or R⁴ is a covalent bond that links (b) to a linker;

R⁵ is hydrogen, hydroxy, or alkoxy;

(iii) a compound of formula (c):

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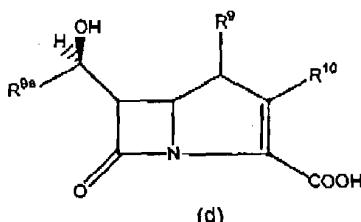
wherein:

T is S or CH₂;

R^{8a} is alkyl;

W is O, S, -OCH₂-, or CH₂; and R⁸ is -(alkylene)-NHC(R^b)=NH where R^b is a covalent bond linking (c) to a linker; or -W-R⁸ is a covalent bond that links (c) to a linker;

(iv) a compound of formula (d):



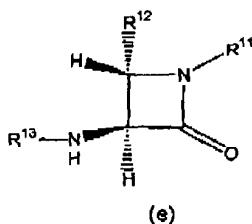
wherein:

R⁸ and R^{9a} are alkyl;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, halo, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl or -CH₂SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (d) to a linker or at least one of R⁹ and R¹⁰ is a covalent bond that links (d) to a linker; or

R⁹ and R¹⁰ together with the carbon atoms to which they are attached form an aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, or heterocyclyl ring of 4 to 7 ring atoms wherein one of the ring atoms optionally links (d) to a linker; or

(v) a compound of formula (e):



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wherein:

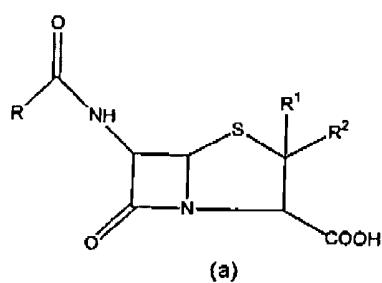
R¹¹ is -SO₃H or -(alkylene)-COOH:

R^{12} is alkyl, substituted alkyl, haloalkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, substituted cycloalkyl, or heterocyclyl wherein each of said substituent optionally binds (e) to a linker or R^{12} is a covalent bond that links (e) to a linker; and

R^{13} is alkyl, acyl, or $-COC(R^{14})=N-OR^{15}$ wherein R^{14} is aryl, heteroaryl which optionally links (e) to a linker, and R^{15} is $-(alkylene)-COOR^{16}$ wherein R^{16} is hydrogen or optionally links (e) to a linker or R^{13} is a covalent bond that links (e) to a linker, preferably

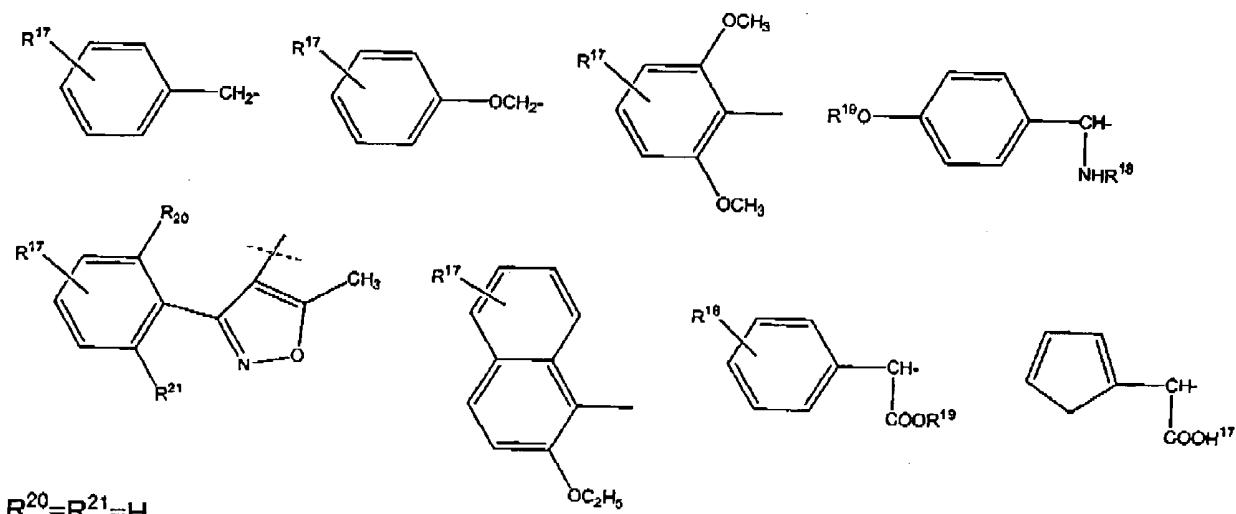
L^a is selected from the group consisting of:

(i) a compound of formula (a):



wherein:

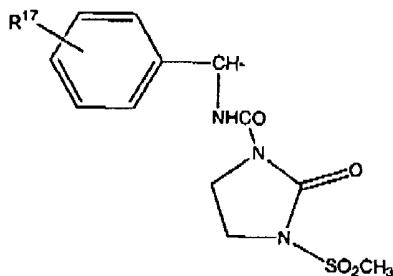
R is:



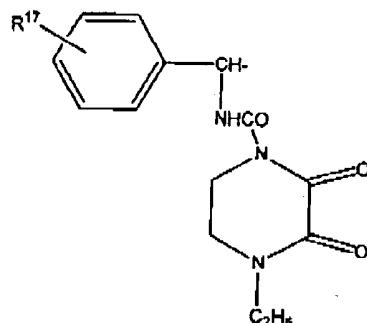
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$R^{20}=R^{21}=Cl$

$R^{20}=Cl$ and $R^{21}=H$



or



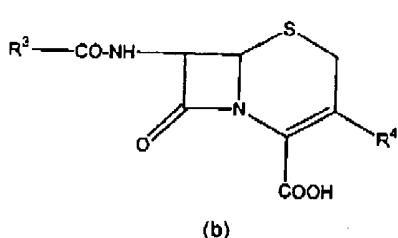
where:

R^{17} is a covalent bond that links the (a) group to a linker;

one of R^{18} and R^{19} is hydrogen and the other is a covalent bond that links the (a) group to a linker; and

R^1 and R^2 are methyl;

(ii) a compound of formula (b):

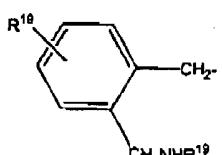
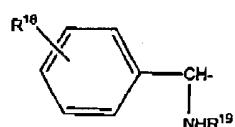
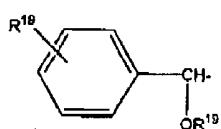
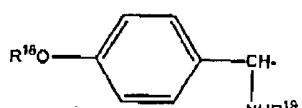
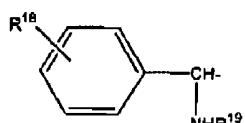
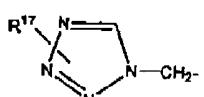
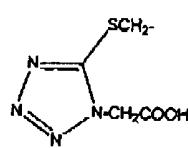
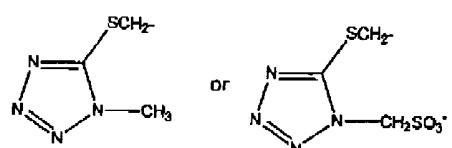
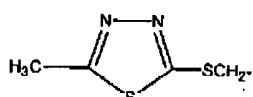


(b)

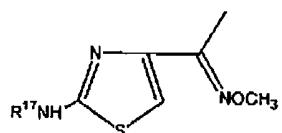
where:

R^3 and R^4 are:

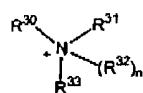
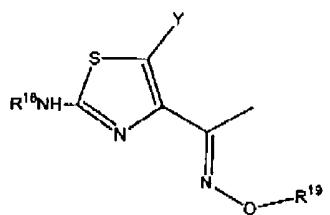
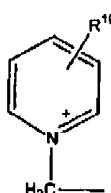
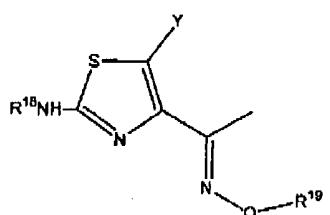
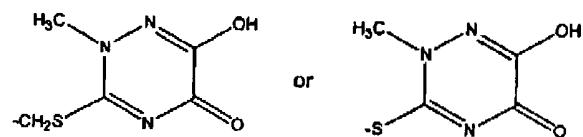
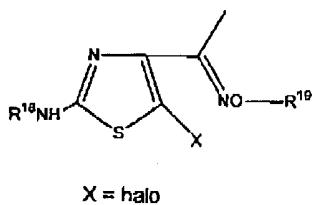
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 R^3  R^4 

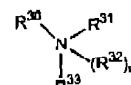
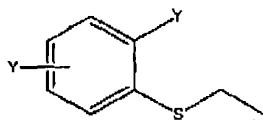
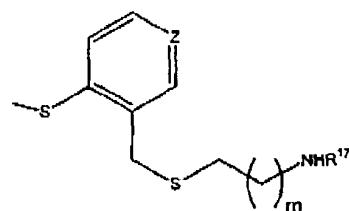
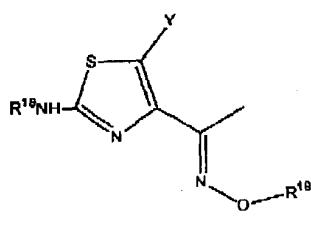
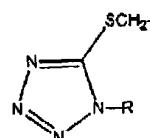
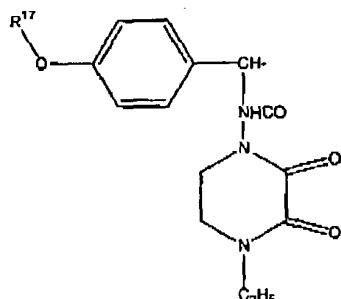
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-CH₂OOCCH₃, -CH₂OCH₃, H



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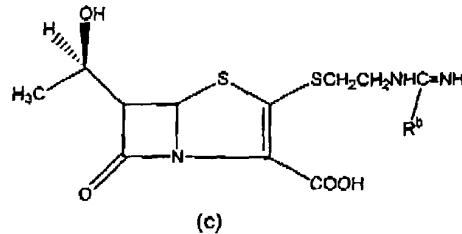


(Note: the R³ group in the left column is paired with the R⁴ in the right column)

wherein:

n is 0 or 1; m is 1-5; Z is CH or N; Y is H or halo; R is alkyl; R¹⁷ is a covalent bond that links the (b) group to a linker; one of R¹⁸ and R¹⁹ is hydrogen or alkyl; R³⁰ and R³¹ are, independently of each other, hydrogen or alkyl; or together with the nitrogen atom to which they are attached form a heterocycloamino group; and R, R³² and R³³ are independently alkyl wherein one of R¹⁸, R¹⁹, R³⁰-R³³ is a covalent bond that links the (b) group to a linker;

(iii) a compound of formula (c):

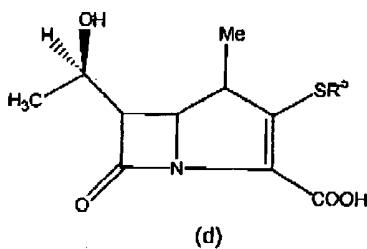


(c)

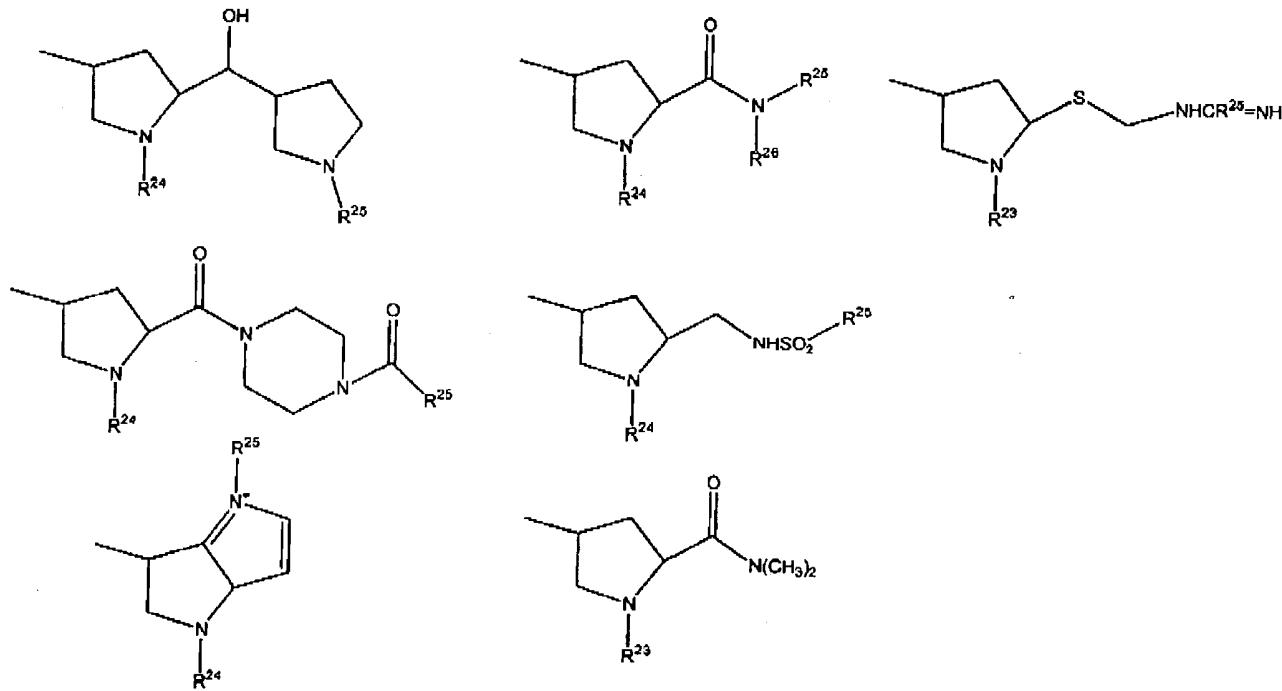
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wherein R^b is a covalent bond linking (c) to a linker;

(iv) a compound of formula (d):



where R^a is:



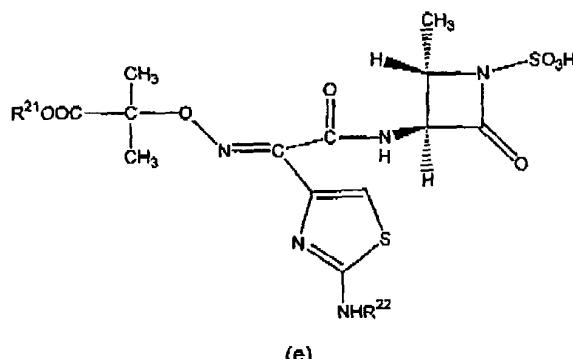
where:

R²³ is a covalent bond that links (d) to a linker;

one of R²⁴ and R²⁵ is hydrogen, alkyl, substituted alkyl, or aralkyl, and
 other is a covalent bond that links (d) to a linker; R²⁶ is alkyl; or

(v) a compound of formula (e):

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(e)

wherein one of R²¹ and R²² is hydrogen and the other links (d) to a linker; [.]

L^b is an optionally substituted vancomycin which is linked to a linker via any hydroxyl group, carboxyl group or amino group; and

X is a linker and is selected from a compound of formula:



wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR-, -NRC(O)-, C(S), -C(S)O-, -C(S)NR-, -NRC(S)-, or a covalent bond where R is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

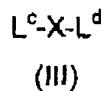
each Y^a at each separate occurrence is selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -NR'C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-, -P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)_nCR'R'', -S(O)_n-NR'-, -NR'-S(O)_n-, -S-S-, and a covalent bond; where n is 0, 1 or 2; and R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic; and pharmaceutically acceptable salts thereof provided that when L^b is vancomycin attached to a linker via the [C] terminus, then L^a cannot be cefalexin

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attached to the linker via acylation of its alpha amino group; and pharmaceutically acceptable salts thereof.

Please amend the paragraph beginning on page 48, line 10 and ending on page 57, line 18 with:

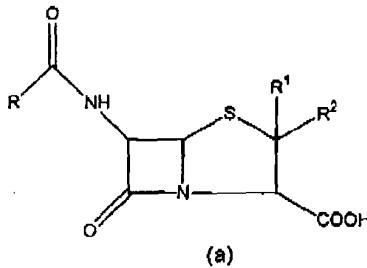
(B) Another more preferred group of compounds is a multibinding compound of Formula (III):



wherein:

ligands, L^c and L^d , are a beta lactam antibiotic and are independently selected from the group consisting of:

(i) a compound of formula (a):



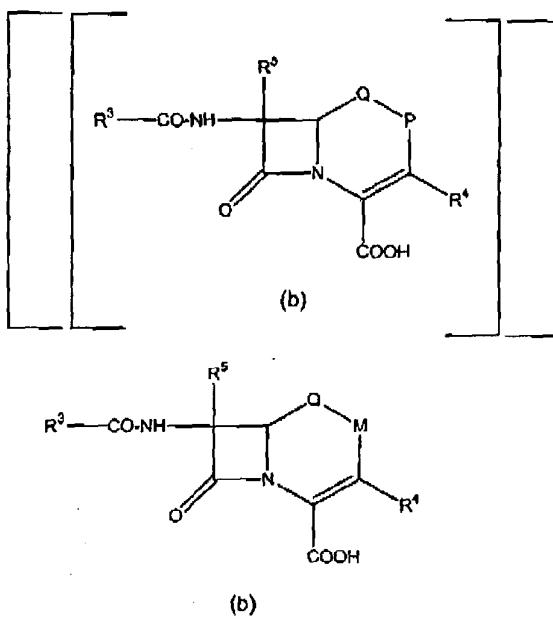
wherein:

R is substituted alkyl, aryl, aralkyl, or heteroaryl wherein each of said substituent optionally links (a) to a linker via a covalent bond or R is a covalent bond that links (a) to a linker; and

R¹ and R² are, independently of each other, alkyl or at least one of R¹ and R² is a covalent bond linking (a) to a linker;

(ii) a compound of formula (b):

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wherein:

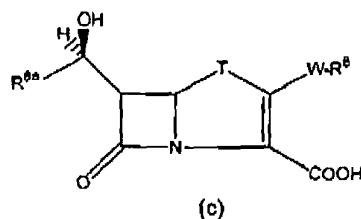
one of [[P]] M and Q is O, S, or $-\text{CH}_2-$ and the other is $-\text{CH}_2-$;

R^3 is substituted alkyl, heteroarylalkyl, aralkyl, heterocyclalkyl, or $-\text{C}(\text{R}^6)=\text{NOR}^7$ (where R^6 is aryl, heteroaryl, or substituted alkyl; and R^7 is alkyl or substituted alkyl) wherein each of said substituent optionally links (b) to a linker or R^3 is a covalent bond that links (b) to a linker; and

R^4 is hydrogen, alkyl, alkenyl, substituted alkenylene, substituted alkyl, halo, heteroarylalkyl, heterocyclalkyl, $-\text{SR}^8$ (where R^8 is aryl, heteroaryl, heterocyclyl, or cycloalkyl) or $-\text{CH}_2\text{SR}^8$ (where R^8 is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (b) to a linker or R^4 is a covalent bond that links (b) to a linker;

R^5 is hydrogen, hydroxy, or alkoxy;

(iii) a compound of formula (c):



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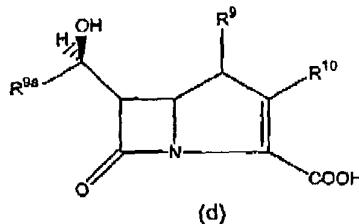
wherein:

T is S or CH₂;

R^{8a} is alkyl;

W is O, S, -OCH₂-, or CH₂; and R⁸ is -(alkylene)-NHC(R^b)=NH where R^b is a covalent bond linking (c) to a linker; or -W-R⁸ is a covalent bond that links (c) to a linker;

(iv) a compound of formula (d):



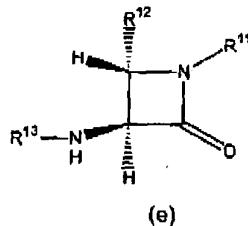
wherein:

R⁹ and R^{9a} are alkyl;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, halo, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl or -CH₂SR^a (where R^a is aryl, heteroaryl, heterocyclyl, or cycloalkyl) wherein each of said substituent optionally links (d) to a linker or at least one of R⁹ and R¹⁰ is a covalent bond that links (d) to a linker; or

R⁹ and R¹⁰ together with the carbon atoms to which they are attached form an aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, or heterocyclyl ring of 4 to 7 ring atoms wherein one of the ring atoms optionally links (d) to a linker; or

(v) a compound of formula (e):



wherein:

R¹¹ is -SO₃H or -(alkylene)-COOH;

R¹² is alkyl, substituted alkyl, haloalkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, substituted cycloalkyl, or heterocyclyl wherein each of said

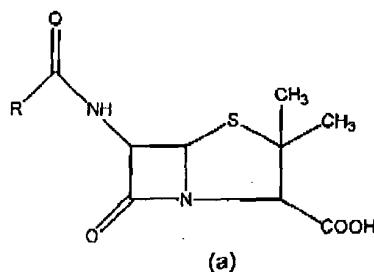
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substituent optionally binds (e) to a linker or R^{12} is a covalent bond that links (e) to a linker; and

R^{13} is alkyl, acyl, or $-COC(R^{14})=N-OR^{15}$ wherein R^{14} is aryl, heteroaryl which optionally links (e) to a linker, and R^{15} is $-(alkylene)-COOR^{16}$ wherein R^{16} is hydrogen or optionally links (e) to a linker or R^{13} is a covalent bond that links (e) to a linker, preferably

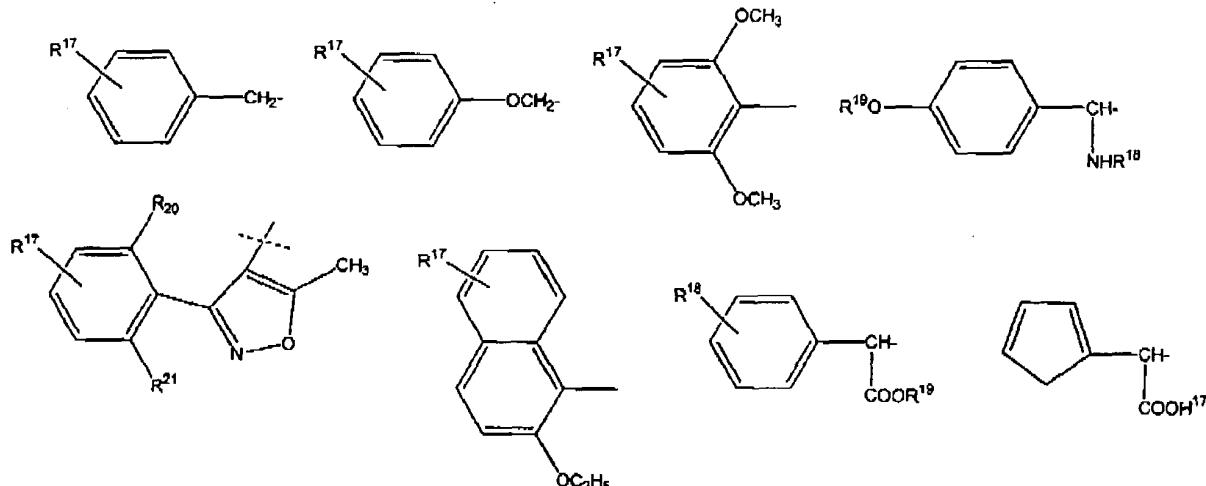
L^c and L^d are independently selected from the group consisting of:

(i) a compound of formula (a):



wherein:

R is:

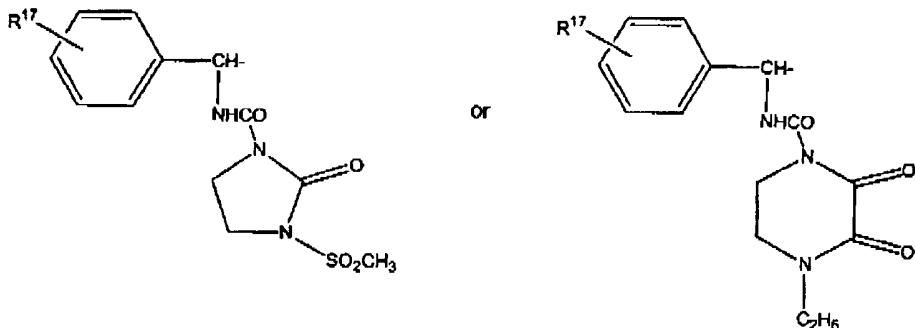


$R^{20}=R^{21}=H$

$R^{20}=R^{21}=Cl$

$R^{20}=Cl$ and $R^{21}=H$

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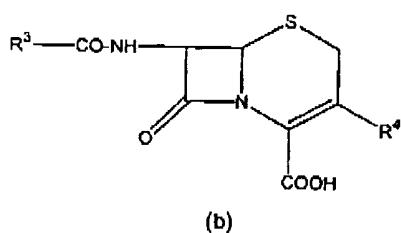


where:

R^{17} is a covalent bond that links the (a) group to a linker;

one of R^{18} and R^{19} is hydrogen and the other is a covalent bond that links the (a) group to a linker; and

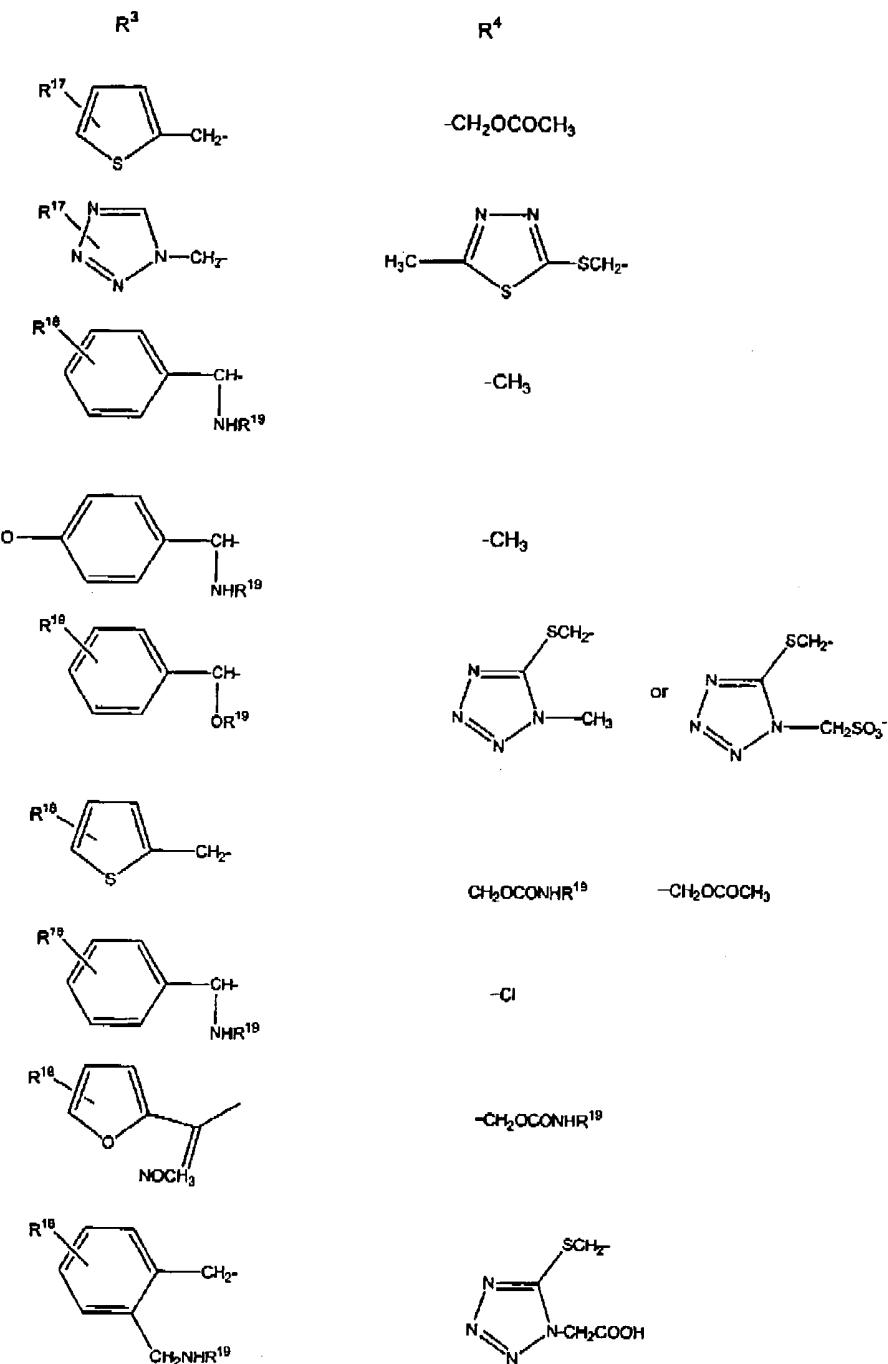
(ii) a compound of formula (b):



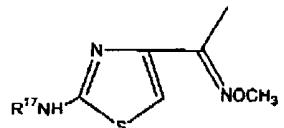
where:

R^3 and R^4 are:

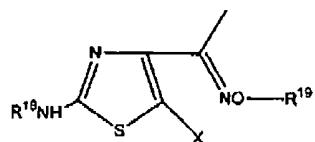
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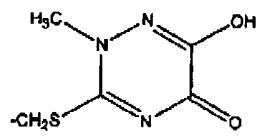
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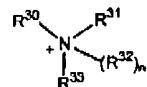
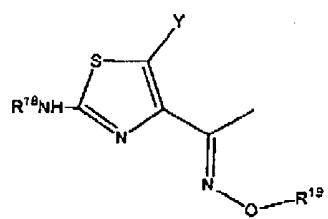
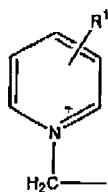
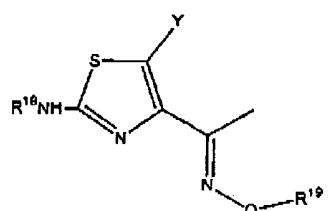
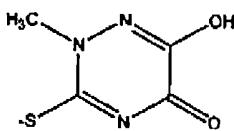
-CH₂OCOCH₃, -CH₂OCH₃, H



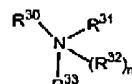
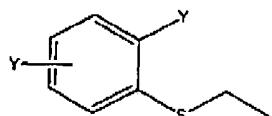
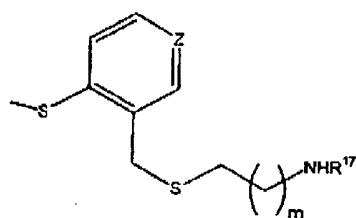
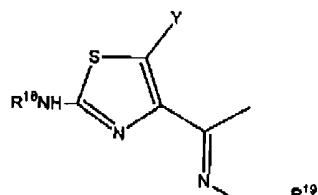
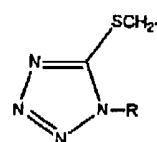
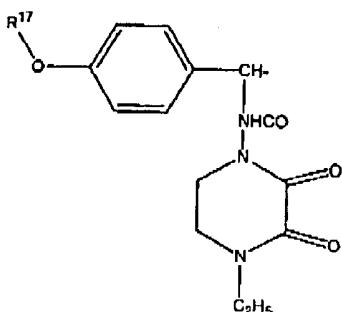
X = halo



or



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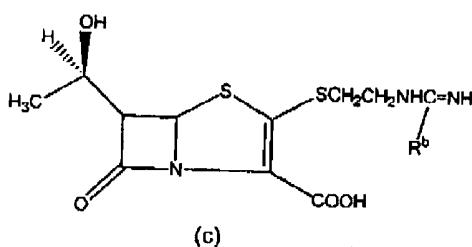
(Note: the R³ group in the left column is paired with the R⁴ in the right column)

wherein:

n is 0 or 1; m is 1-5; Z is CH or N; Y is H or halo; R is alkyl;

R¹⁷ is a covalent bond that links the (b) group to a linker; one of R¹⁸ and R¹⁹ is hydrogen or alkyl; R³⁰ and R³¹ are, independently of each other, hydrogen or alkyl; or together with the nitrogen atom to which they are attached form a heterocycloamino group; and R, R³² and R³³ are independently alkyl wherein one of R¹⁸, R¹⁹, R³⁰-R³³ is a covalent bond that links the (b) group to a linker;

(iii) a compound of formula (c):



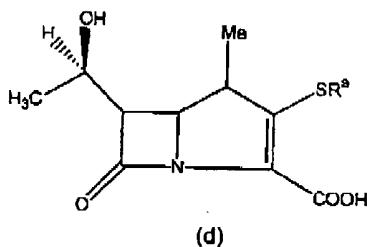
wherein R^b is a covalent

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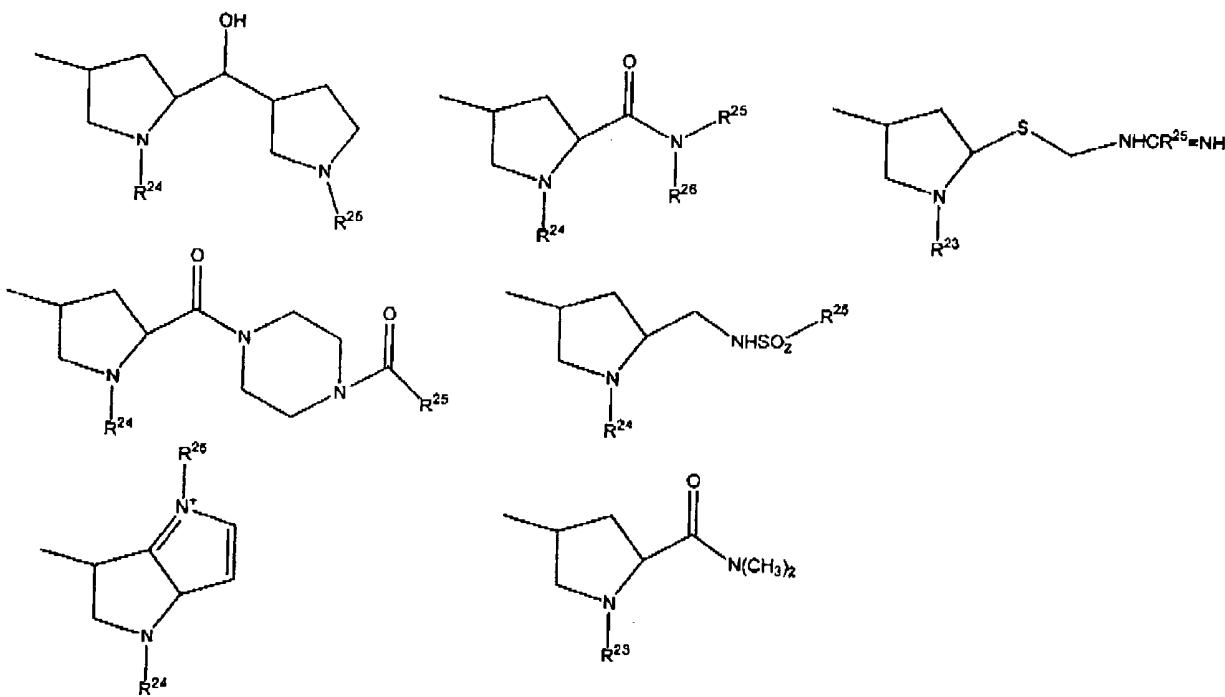
bond linking (c) to a linker;

(iv) a compound of

formula (d):



where R^a is:



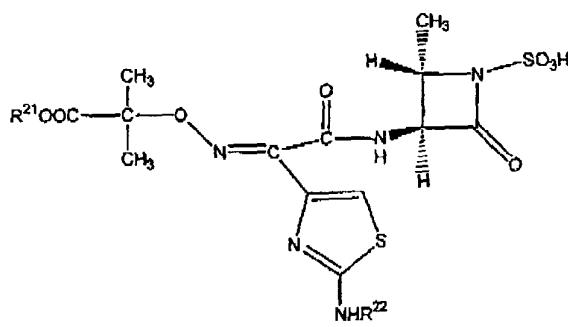
where:

R²³ is a covalent bond that links (d) to a linker;

one of R²⁴ and R²⁵ is hydrogen, alkyl, substituted alkyl, or aralkyl, and
 other is a covalent bond that links (d) to a linker; R²⁶ is alkyl; or

(v) a compound of formula (e):

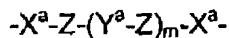
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(e)

wherein one of R²¹ and R²² is hydrogen and the other links (d) to a linker; and

X is a linker is selected from a compound of formula:



wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR-, -NRC(O)-, C(S), -C(S)O-, -C(S)NR-, -NRC(S)-, or a covalent bond where R is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

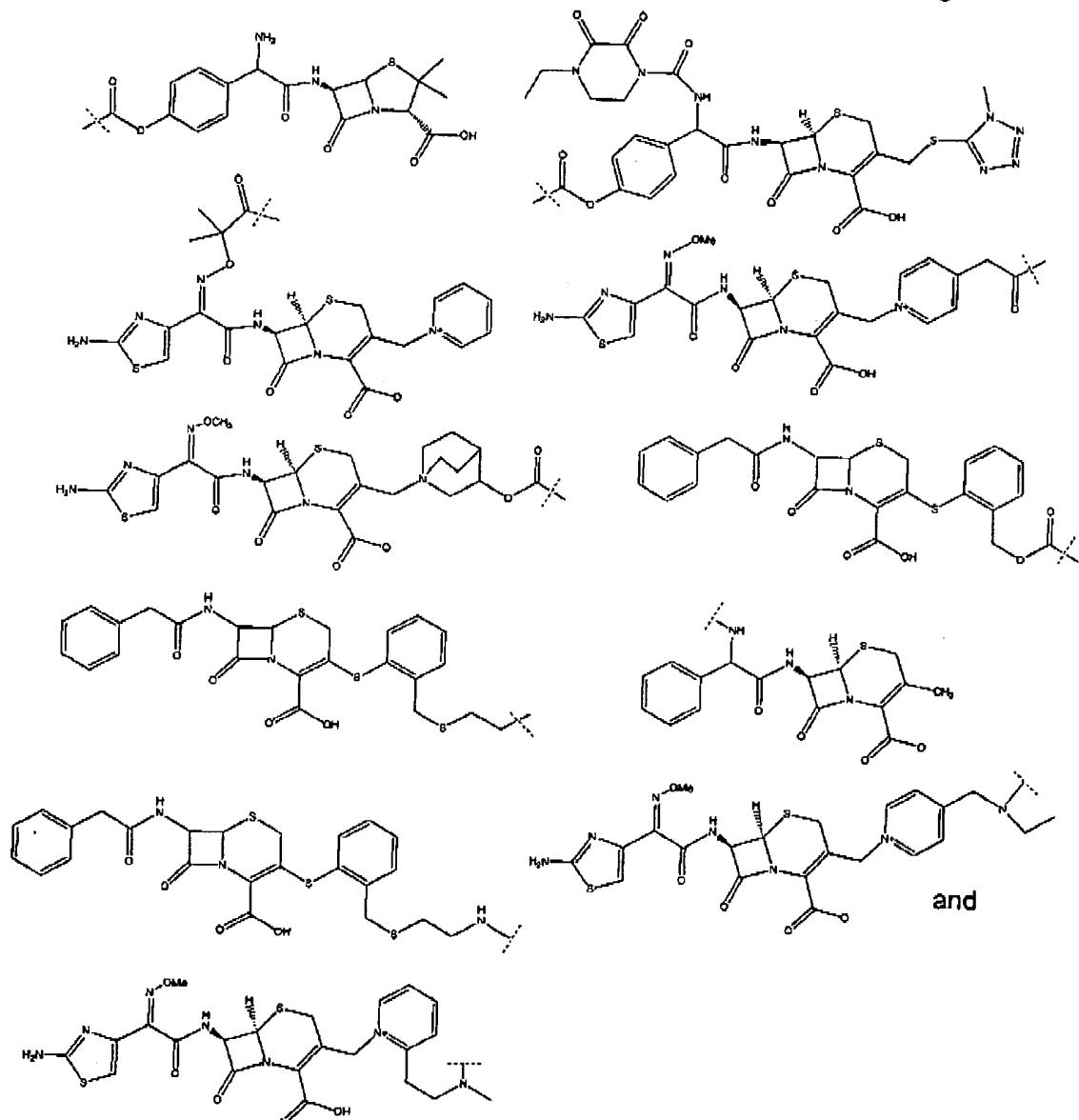
each Y^a at each separate occurrence is selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -NR'C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-, -P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)_nCR'R"-, -S(O)_n-NR'-, -NR'-S(O)_n-, -S-S-, and a covalent bond; where n is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic; and pharmaceutically acceptable salts thereof.

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Please amend the paragraph beginning on page 57, line 20 and ending on page 80 with:

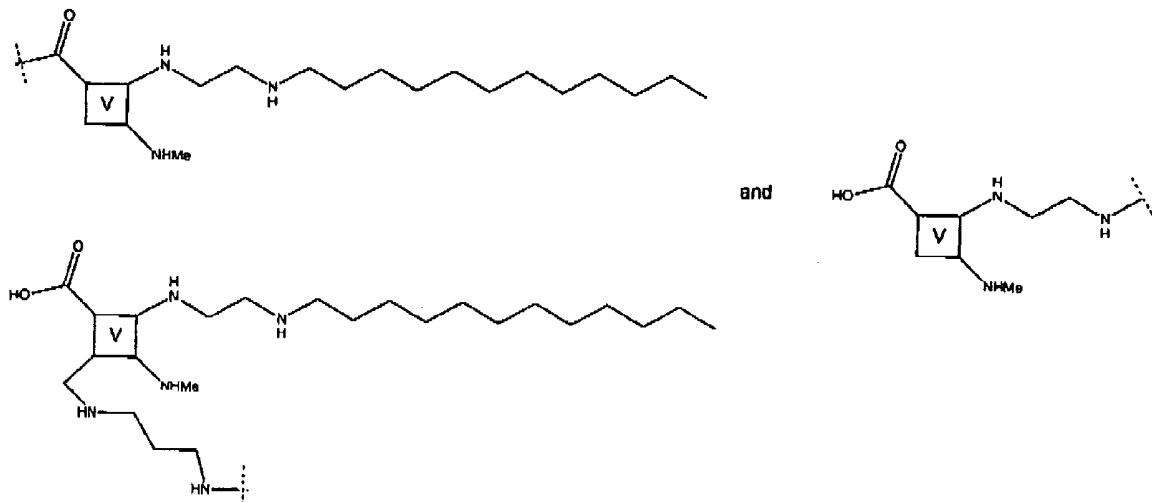
Within the above more preferred groups, an even more preferred group of compounds is that wherein:

L^a , L^c , and L^d are independently selected from the group consisting of:



L^b is selected from the group consisting of:

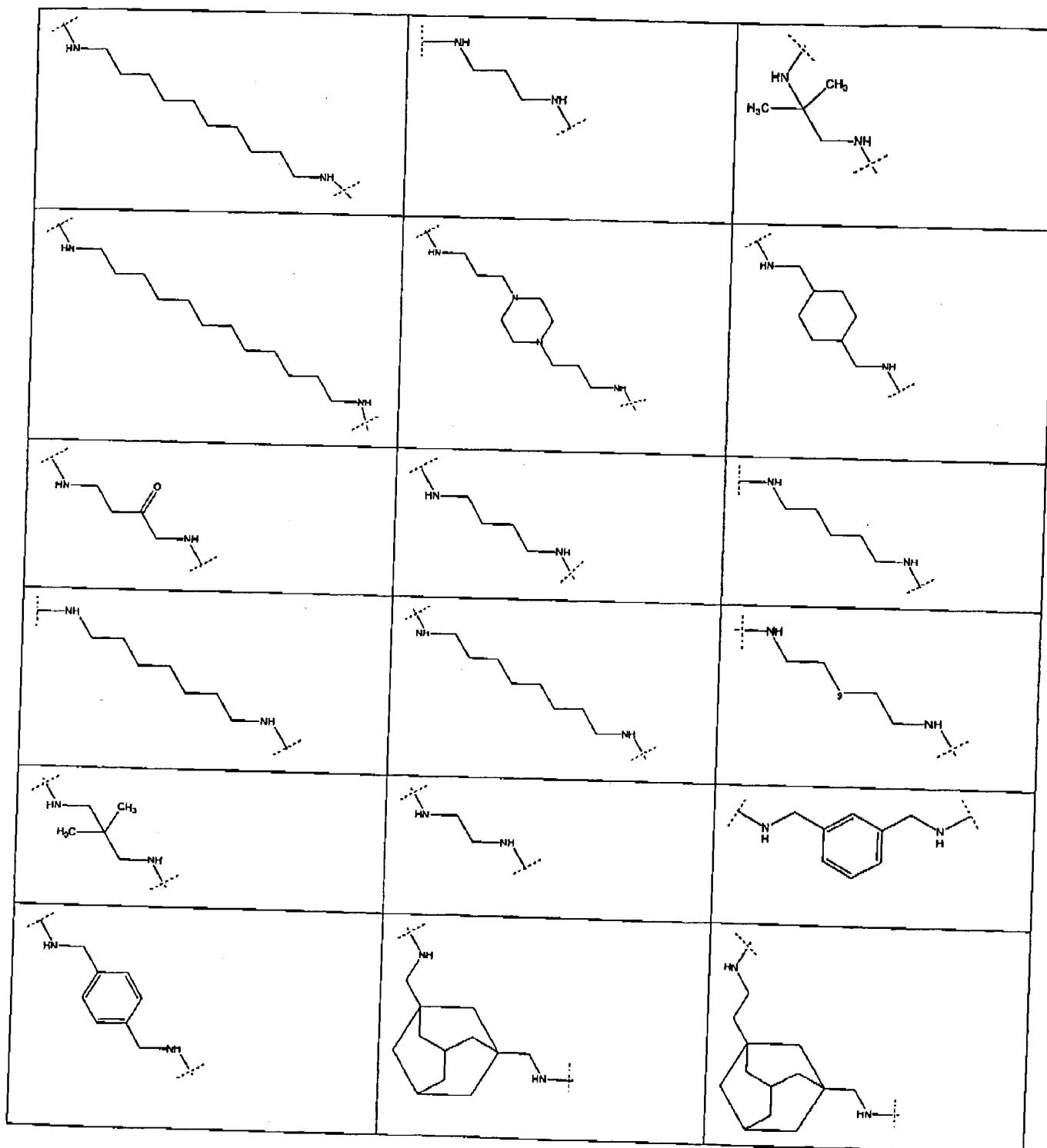
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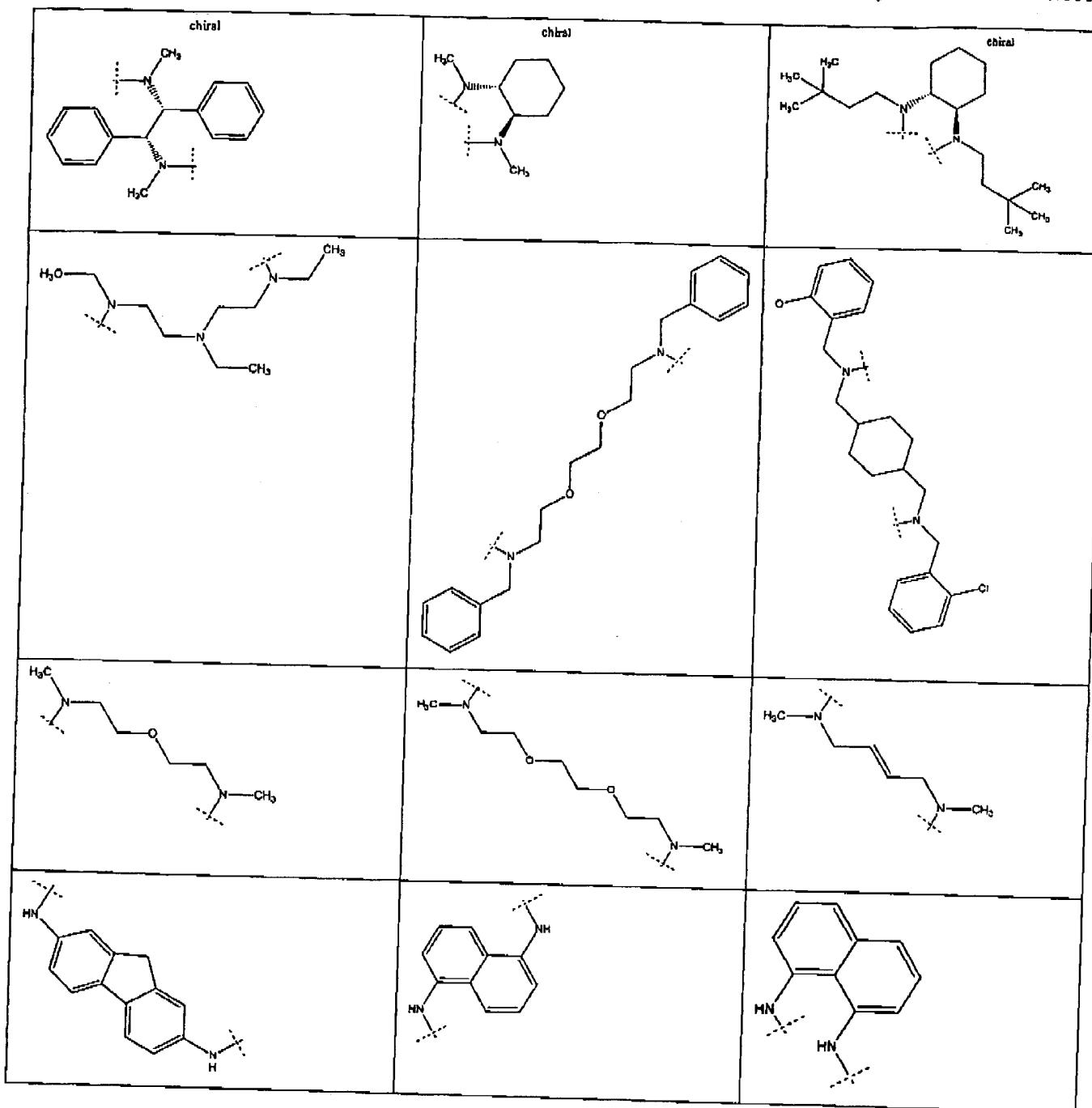
wherein the atom carrying the bond with the dashed line indicates the point of attachment of the ligand to the linker; and

the linker is selected from the group consisting of:

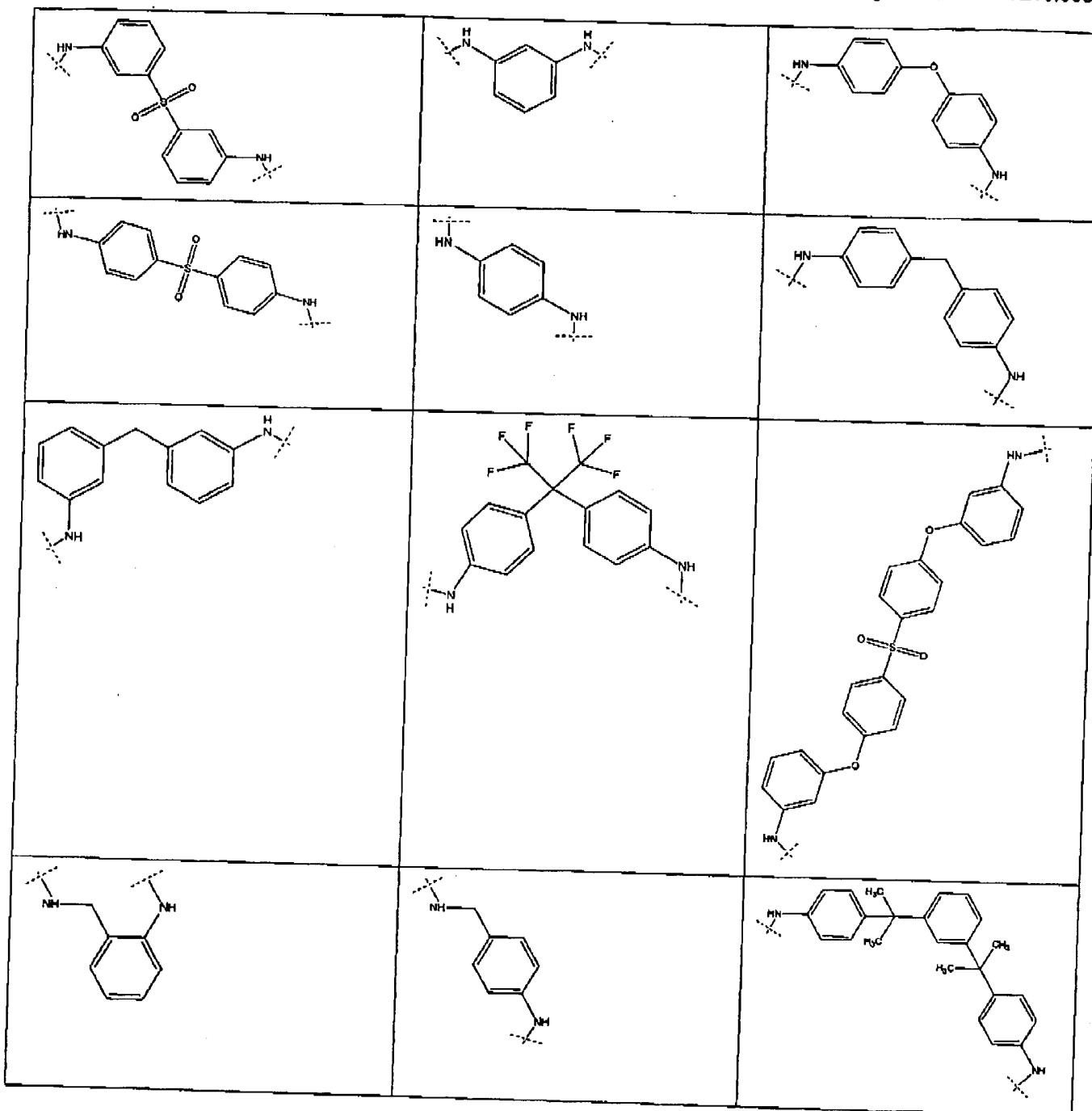
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DIAMINES

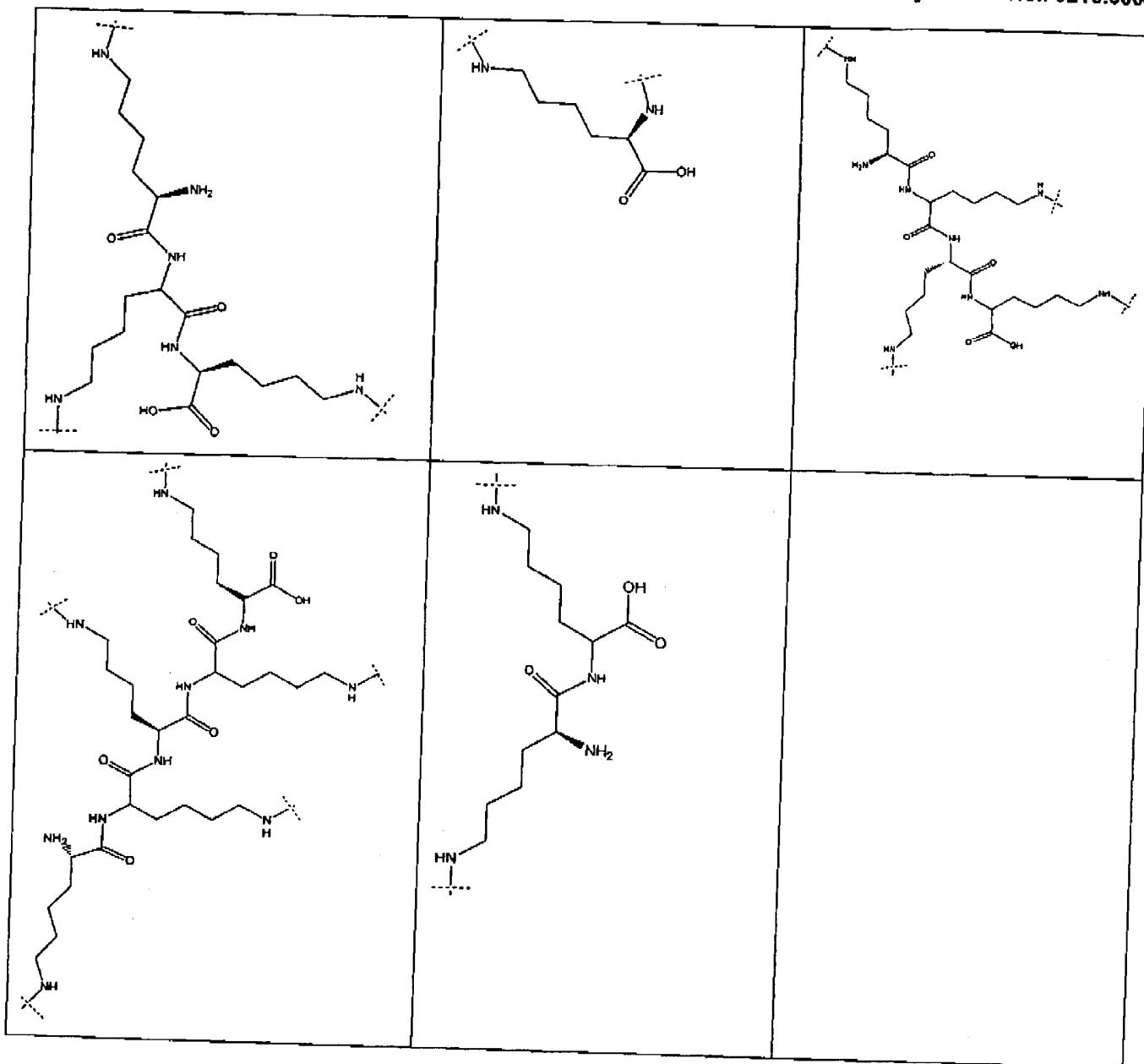
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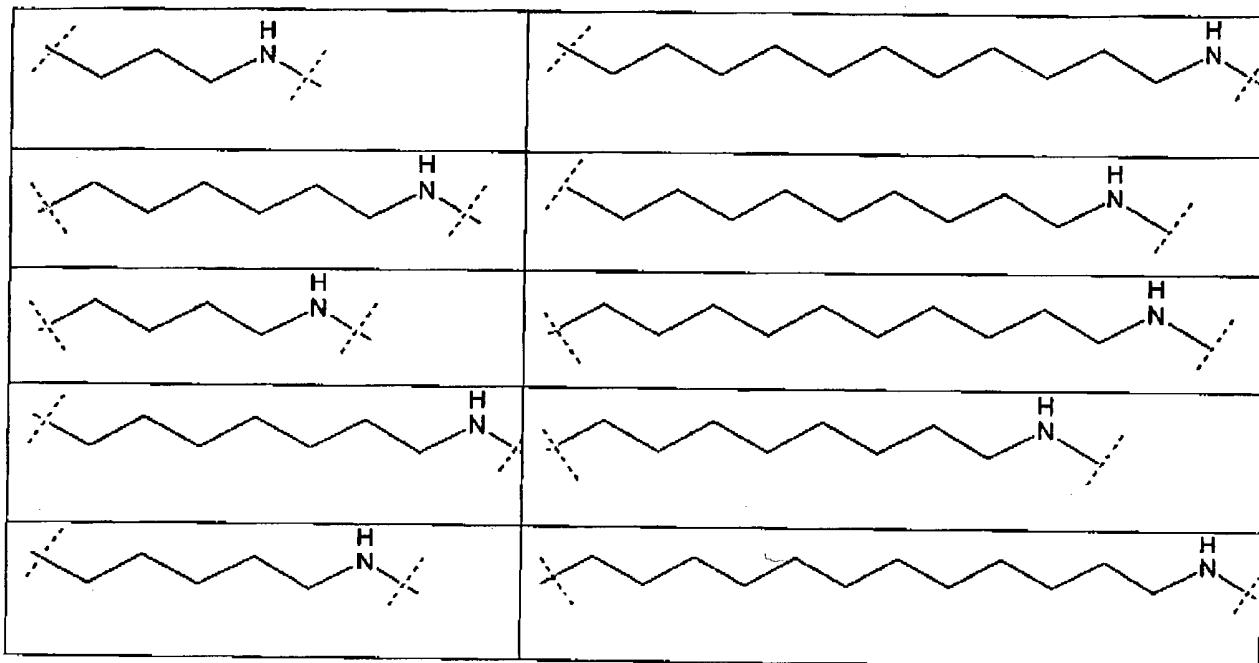


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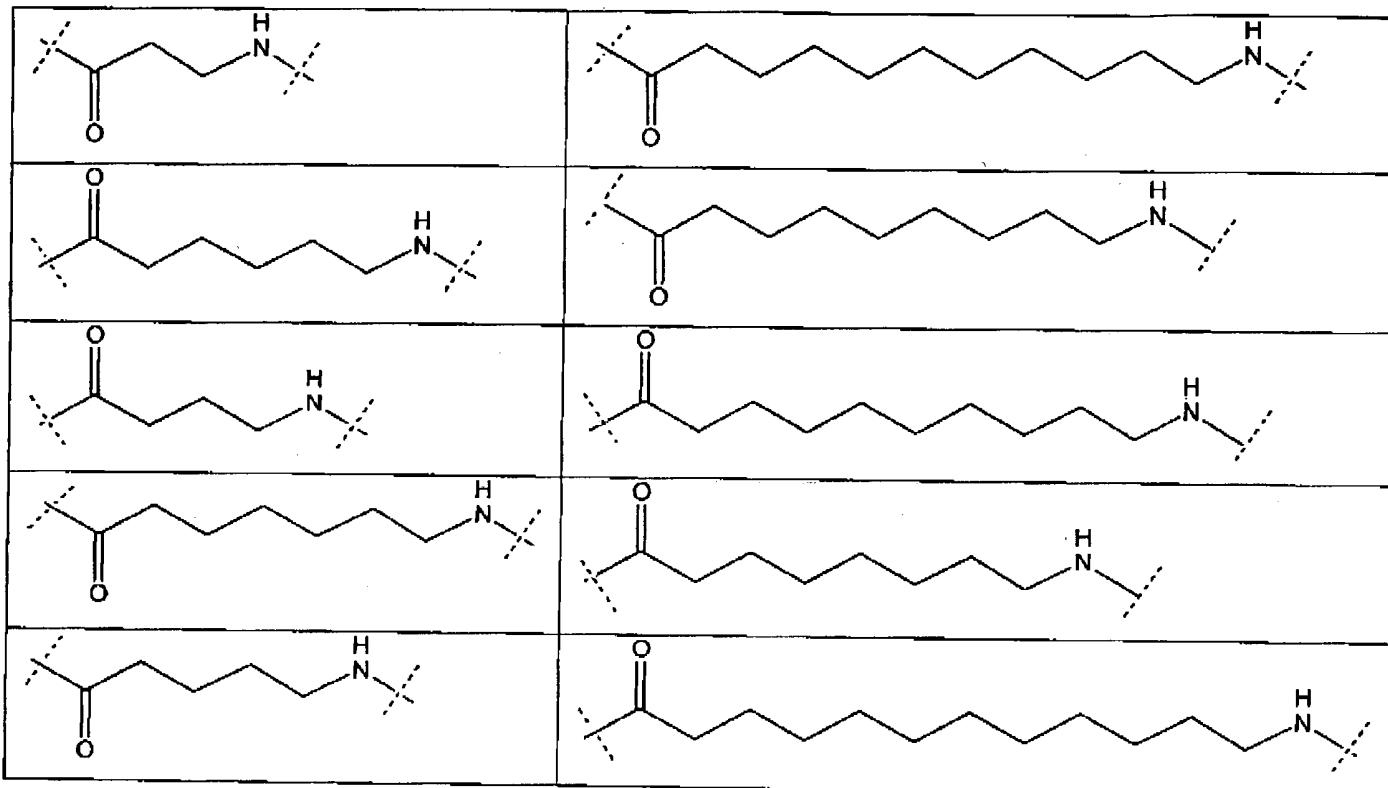
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LINKERS DERIVED FROM AMINOALDEHYDES



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Attorney Docket No.: 9210.0004-00

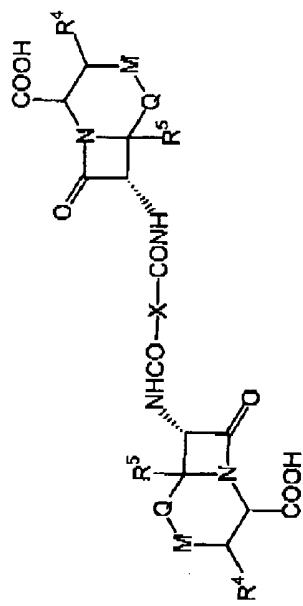
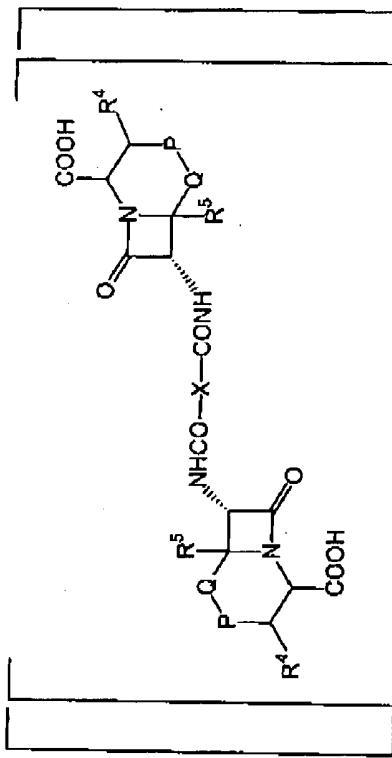
LINKERS DERIVED FROM AMINOACIDS



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Representative compounds of the invention are shown in the table below:

(i) Compounds of Formula (III) wherein the ligands are selected from a compound of formula (b) and are linked to a linker, X, via the R³ group and where [IPI], Q, R⁴, and R⁵ and are as defined below are:



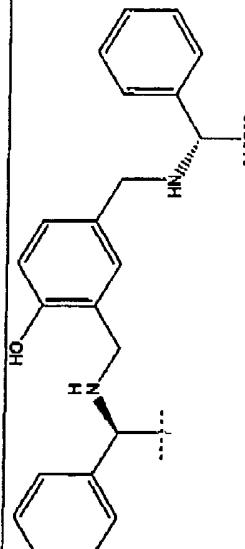
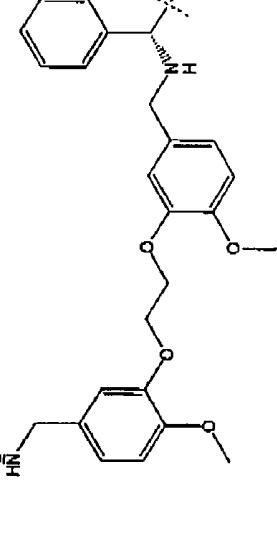
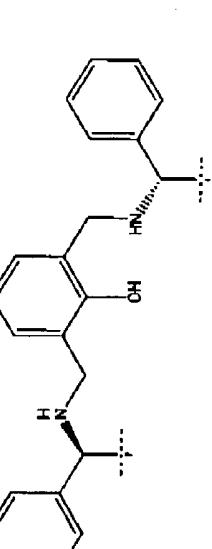
Cpd	Linker X	[IPI] M	Q	R ⁴	R ⁵

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CH ₃	H	-CH ₂ -	S	S	H	-CH ₂ -	S
CH ₃	CH ₃	H	-CH ₂ -	H	CH ₃	H	-CH ₂ -
1	2	3	4				

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S	S	S
H	-CH ₂ -	H
CH ₃	H	CH ₃
		
5	6	7

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	CH ₃	H	-CH ₂ -
			S
8			
9			
10			
11			

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	CH ₃	H	-CH ₂ -	S		CH ₃	H	-CH ₂ -	S		CH ₃	H	-CH ₂ -	S
12														
13														
14														

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S		S	
-CH ₂ -	H	-CH ₂ -	H
-CH ₂ -1-methyl-1H-tetrazol-5-ylsulfanyl		-CH ₂ -1-methyl-1H-tetrazol-5-ylsulfanyl	
15		16	

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	-CH ₂ -	S
	H	
	-CH ₂ -1-methyl-1H-tetrazol-5-ylsulfonyl	-CH ₂ -1-methyl-1H-tetrazol-5-ylsulfonyl
17		
18		

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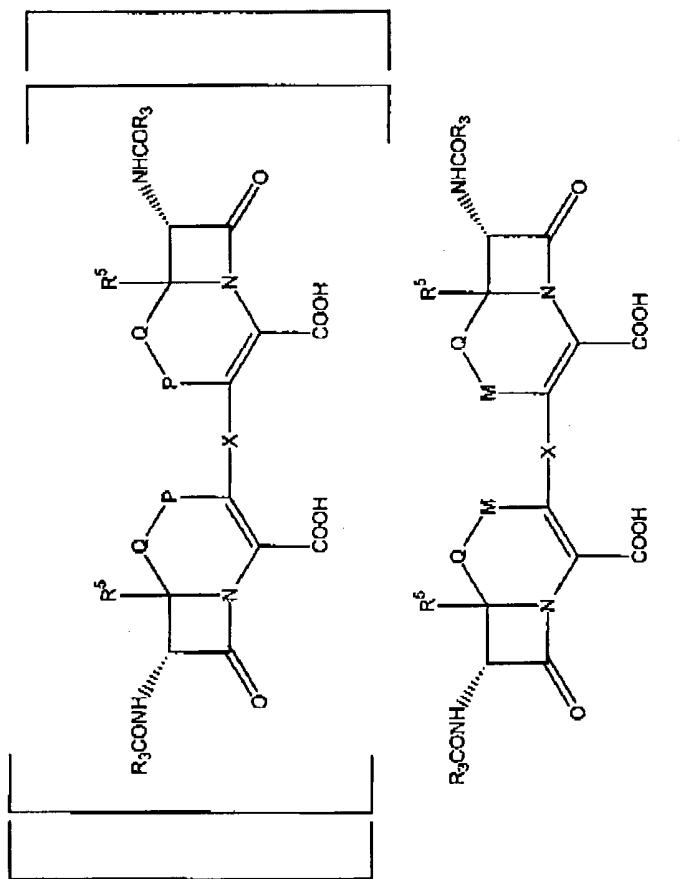
		S	
	-CH ₂ -r		
	H		
-CH ₂ -1- methyl-1H- tetrazol-5- ylsulfanyl			
19			
	-CH ₂ -r		
	H		
-CH ₂ -1- methyl-1H- tetrazol-5- ylsulfanyl			
20			

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	-CH ₂ -	H	-CH ₂ -	S
	-CH ₂ -1-methyl-1H-tetrazol-5-ylsulfanyl			
21				
22				

(III) Compound of Formula (III) wherein the ligands are selected from a compound of formula (b) and are linked to a linker, X, via the R⁴ group and where [I] M, Q, R³, and R⁵ and are as defined below are:

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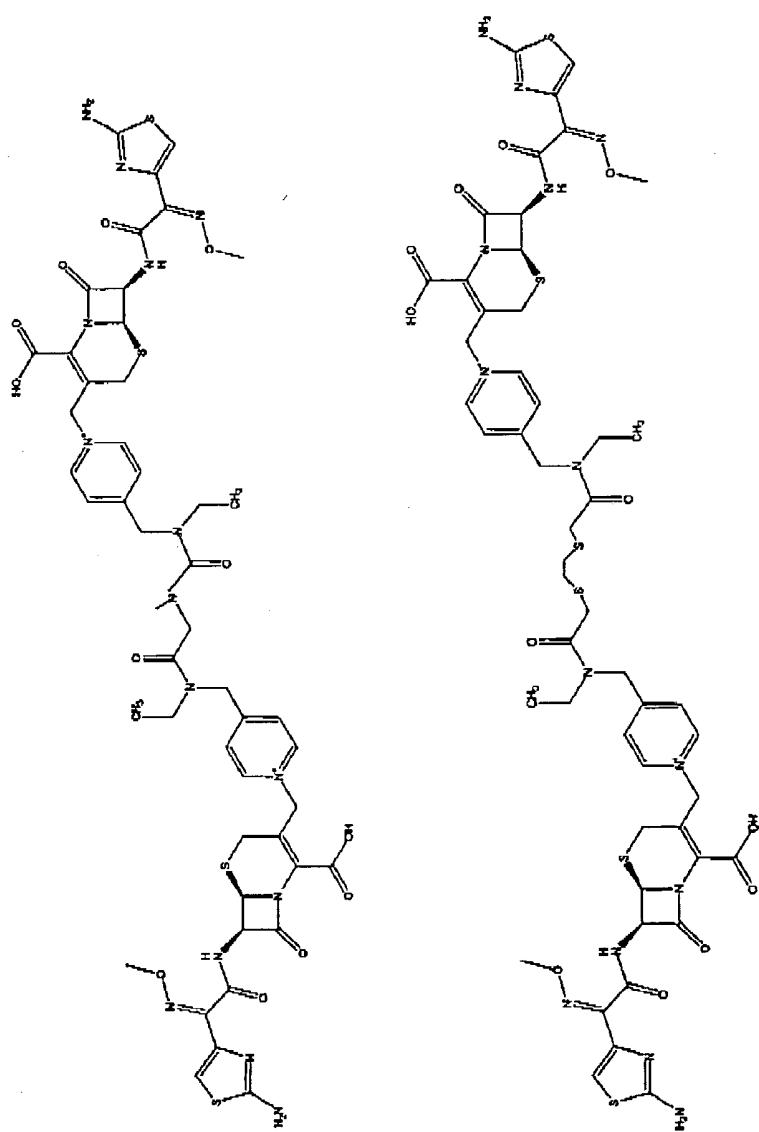


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Cp d No	Linker X	[[P]] M	Q	R ³	R ⁵
1		(2-aminothiazol-4-yl)-methoxyiminoethyl	H	-	S CH ₂ -

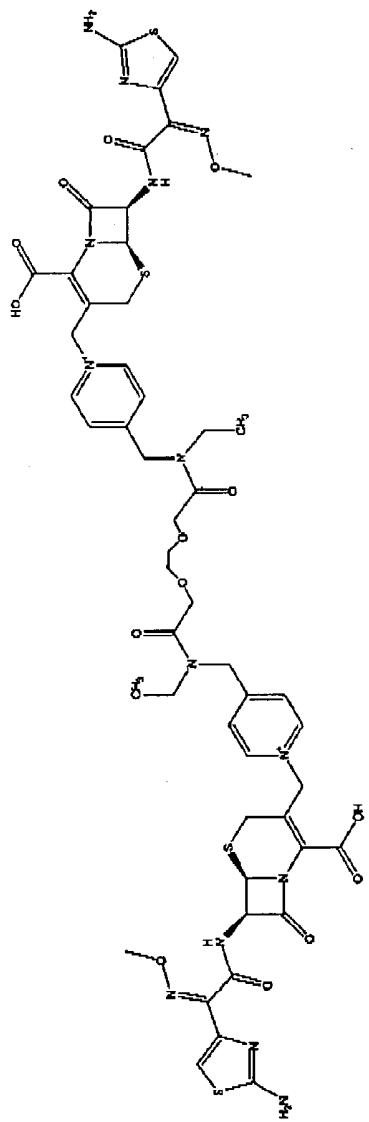
III. Other compounds of the invention are:

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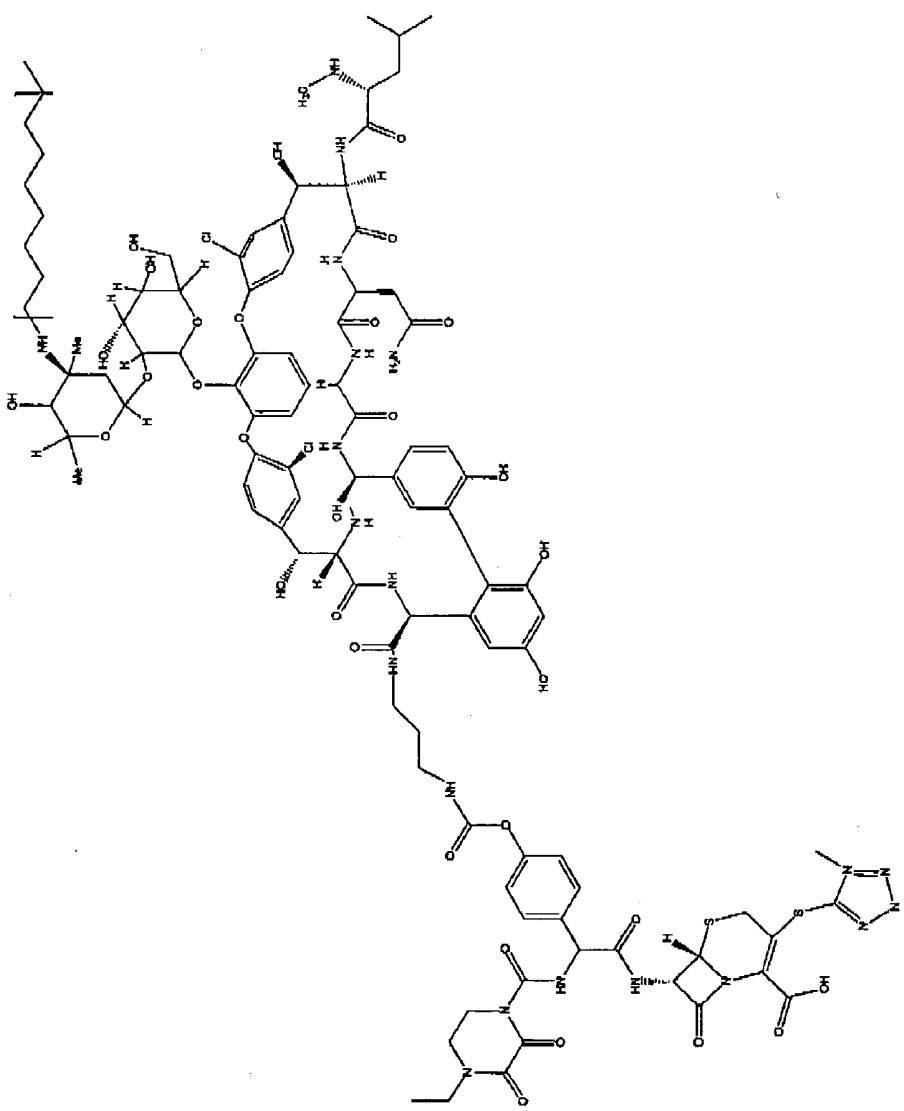
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